REMARKS

I. Status of the Claims

Claims 1-3, and 8-10 are currently under examination on their merits. Claims 4-7, 11-49 are canceled without disclaimer or prejudice against the prosecution of the claims in future continuation or divisional applications. Claim 3 is amended. Support for the amendment can be found throughout the specification as originally filed, for example, on page 96, last paragraph to page 97, first paragraph. Thus, the amendment does not introduce new matter.

II. Previous Claim Rejections Under 35 U.S.C. §§ 102(b) and 103(a)

Applicants acknowledge with thanks withdrawal of previously-asserted rejections under 35 U.S.C. §§ 102(b) and 103(a).

III. Claim Rejection Under 35 U.S.C. §112, First Paragraph, Enablement

Claims 1-3 and 8-10 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to satisfy the enablement requirement. The Examiner asserts that the specification, while enabling a method of inhibiting tumor proliferation *in vitro*, it does not enable a method of inhibiting tumor proliferation *in vivo*. Applicants respectfully traverse.

An analysis of enablement requires a determination of whether the specification contains sufficient information regarding the subject matter of the claims so as to enable one skilled in the art to make and use the claimed invention, without undue experimentation. MPEP §2164.01. (emphasis added) A key issue that can arise is whether the starting materials or apparatus necessary to make the invention are available. MPEP §2164.01(b). With respect to how to use the claimed invention, the court has held that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC §112 is satisfied. M.P.E.P.2164.01(c). *See In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960). *See also In re Brana*, 51 F.2d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Applicants submit that the claims are fully enabled by the specification because the specification teaches one of skill in the art how to make and use the claimed invention without undue experimentation, that Applicants are not required to present *in vivo* testing data; and that the *in vitro* results reasonably correlate with the *in vivo* results.

1. **The specification teaches how to make and use the anti-tumor p19ARF protein fragment both *in vitro* and *in vivo*.**

The specification teaches the anti-tumor activity of p19ARF protein. The specification describes that FoxM1B is required for hepatic tumor progression in an *in vivo* mouse tumor model (Example 9). The specification demonstrates that endogenous p19ARF protein interacts with FoxM1B protein *in vivo* (Example 15). The region spanning amino acid residues 26-44 of the p19ARF protein was identified as the region sufficient for binding to FoxM1B protein, and inhibiting FoxM1B transcriptional activity (Example 18). Further, the specification shows that the p19ARF 26-44 peptide fused to a cell-penetrating arginine-rich peptide, as identified by SEQ ID NO:10, penetrated into cells upon contacting the cells (Example 20). Once inside the cell, the p19ARF protein fragment was localized in the nucleolus and targeted FoxM1B to the nucleolus (Figure 16L, and page 96, Example 19). The specification further demonstrates that cells contacted with the p19ARF26-44 peptide exhibited reduced levels of colony formation, the hallmark of tumorogenesis (Example 17 and Figure 17).

The specification teaches, and it is also within the knowledge of one of skilled in the art, how to make the p19ARF protein fragment having the amino acid sequence as set forth in SEQ ID NO:10 (Page 91, Example 16). The specification discloses a pharmaceutical composition comprising the p19ARF protein fragment for inhibiting tumor growth (Page 52, first paragraph). The dose range of the peptide for *in vivo* treatment is taught in the specification and is also within the knowledge of one of skill in the art and can be determined by routine practice (page 59, last paragraph). The pharmaceutical composition can be administered into an animal by standard intraperitoneal (i.p.) injection (Page 60, second paragraph). Thus, the specification tells a skilled artisan all he needs to know in order to carry out the invention. Thus, the specification not only provides the starting material, but also teaches a person skilled in the art how to carry out the claimed method for inhibiting tumor growth both *in vitro* and *in vivo*.

2. **It is not incumbent upon Applicants to provide *in vivo* testing data.**

The Examiner based the enablement rejection on the assertion that the specification does not disclose "the inhibition of tumor cell proliferation *in vivo* by the p19ARF protein fragment of SEQ ID NO:10." Applicants respectfully submit that there is simply no requirement that a specification contain evidence of actual reduction to practice; indeed, filing a patent application is constructive reduction to practice and has sufficed to satisfy the enablement requirements for

over a century. *Dolbear v. American Bell Telephone Co.*, 126 U.S. 1 (1888); *U.S. v. American Bell Telephone Co.*, 128 U.S. 315 (1888); *In re Borkowski*, 164 USPQ 642 (CCPA 1970); *In re Strahilevitz*, 212 USPQ 561 (CCPA 1982).

Further, there is no authority requiring the utility of a pharmaceutical active substance be proved by *in vivo* testing. See *In re Isaacas*, 347 F.2d 887, 890, 146 USPQ 193, 195 (CCPA 1965). Under 35 USC §112 and Patent Office rules, Applicants' assertion of enablement in the specification must be accepted, unless the Examiner can make out a *prima facie* case of non-enablement. Applicants are not obligated to provide any evidence, much less *in vivo* evidence, that the claimed methods are operative, in the absence of a *prima facie* case of non-enablement.

Applicants respectfully submit that the Office has not met its initial burden of establishing a *prima facie* showing of non-enablement. The Examiner asserted that the disclosure "does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability." The court has held that with respect to the *in vitro/in vivo* correlation, a rigorous or an invariable exact correlation is not required, so long as there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity. *See Cross v. Iisuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). Even if the Examiner has evidence that the model does not reasonably correlate, which is not the case here, the Examiner must still weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

The disclosure teaches one skilled artisan how to make and use the claimed invention, and thus fully satisfies the enablement requirement under the statute. In requiring evidence of *in vivo* efficacy, the Patent Office essentially has encroached on the realm of FDA. Unlike seeking drug approval, the patent application process does not require Applicants provide further evidence of *in vivo* operativeness and efficacy of the claimed invention. The Court of Customs and Patent Appeals has held that, "in the usual case where the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry, operativeness is not questioned, and no further evidence is required." *In re Gazave*, 154 USPQ 92, 96 (CCPA 1967). The court has explicitly rejected the position that it is incumbent on the applicant to come forward with evidence that the compounds will function as stated in the application. *Id.* The

court recognized in some situation, for example, if the alleged operation seems clearly to conflict with a recognized scientific principle, or where the device involved was of such a nature that it could not be tested by any known scientific principles, it would be incumbent on the applicant to demonstrate the workability and utility of the device and make clear the principles on which it operates. *Id.*

In this case, however, a method for inhibiting *in vivo* tumor proliferation using a biological compound, such as a peptide, by itself does not suggest any inherently unbelievable undertaking or involve implausible scientific principles. *See Id.* The art cited by the Examiner does not state otherwise. Thus, it is not incumbent upon the Applicants to come forward with evidence of operativeness because the claimed invention conforms to the known principles in the art and can be readily understood by one of skill in the art.

3. Co-inventor Wang's declaration further supports enablement.

In order to expedite prosecution, however, Applicants herewith submit a Declaration under 37 CFR §1.132 by co-inventor Dr. I-Ching Wang. In his declaration, Dr. Wang testifies that he is both a co-inventor of the instant application (Declaration, paragraph 3) and a co-author of a peer-reviewed, scientific journal article published after the filing date of the instant application (Gusarova *et al.* A cell-penetrating ARF peptide inhibitor of FoxM1 in mouse hepatocellular carcinoma treatment, 2007, 117:99-111; Declaration, paragraph 4). Dr. Wang testifies that the *in vivo* experiments disclosed in this reference were conducted following the disclosure of the instant application (Declaration, paragraph 4). He further testifies that the claimed p19ARF peptides of the invention were used in the experiments disclosed in the reference and displayed *in vivo* anti-tumor activity. Dr. Wang testifies that p19ARF 26-44 peptide of the invention was injected intraperitoneally into tumor-bearing mice, penetrated into liver cells *in vivo* and altered Foxm1 cellular localization *in vivo* (Declaration, paragraph 6). Dr. Wang also testifies that p19ARF 26-44 peptide of the invention inhibited hepatocellular tumor proliferation *in vivo*. (Declaration, paragraph 7) Dr. Wang further testifies that the anti-tumor effect of p19ARF26-44 peptide of the invention observed *in vivo* is a result of increased apoptosis induced by the peptide *in vivo*. (Declaration, paragraphs 8 and 9) In conclusion, Dr. Wang testifies that the experimental results described in the instant application correlate with the *in vivo* data disclosed in the reference. (Declaration, paragraphs 10 and 11) Thus, the post-filing

data further supports Applicants' contention that the specification enables both *in vitro* and *in vivo* method of inhibiting tumor proliferation by contacting the cell with the peptide.

The Federal Circuit has approved use of later publication as evidence of the state of art existing on the filing date of the application. *Plant Genetic Systems, N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1342 (Fed. Cir. 2003) (*citing In re Hogan*, 559 F. 2d 595, 605 (CCPA 1977)). Therefore, if the post-filing date publication shows that the specification enables the invention at the time of filing, then the application satisfies the enablement requirement. Thus, as long as the *in vivo* data presented in the post-filing date publication was obtained by following the teachings of the specification, the post-filing date data can be used to show that the specification enables one skilled in the art to make and use the invention. *Cf. Enzo Biochem. Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1376 (Fed. Cir. 1999) (rejecting post-filing date data as proof of enablement because the patentee "did not prove that the alleged post-filing successes were accomplished by following the teachings of the specifications.").

In this case, the post-filing date *in vivo* data supports enablement of the specification because the data was obtained following the teachings of the specification. Dr. Wang testified that the mouse strain C57BL/6 used in the *in vivo* experiments in establishing the *in vivo* mouse tumor model is the same strain of mouse used in the Example 9 of the specification (See paragraph 10 of the Declaration). The *in vivo* results were obtained by injecting the mice with the p19ARF peptide having the sequence of SEQ ID NO:10 disclosed in the specification. The mice were injected by i.p. injection following the teaching of the specification (See page 60, line 12 of the specification). The peptide dosage tested *in vivo* (0.1-10 mg/kg) is well within the *in vivo* dosage range taught in the specification (See page 59, last paragraph of the specification, and paragraph 10 of the Declaration). The post-filing date data and success was obtained following the teachings of the specification, and thus can be used to further support enablement. Accordingly, the specification would have enabled one of skill in the art, at the time of filing, to make and use the claimed method for inhibiting tumor growth *in vivo*.

Based on the foregoing, Applicants respectfully submit that the enablement requirement has been fully met. Reconsideration and withdrawal of the rejection under 35 USC 112, first paragraph is thus respectfully requested.

IV. Conclusions

Applicants respectfully submit that all conditions of patentability are satisfied in the pending claims. Allowance of the claims is thereby respectfully solicited.

The Examiner in charge of this application is invited to contact the undersigned representative as indicated below if it is believed to be helpful.

Respectfully submitted,

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By: /Yijan Elaine Chang/
Yijan Elaine Chang
Reg. No. 54,698

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Ste 3100
Chicago, IL 60606
Telephone: (312) 913-0001
Facsimile: (312) 913-0002